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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,156	02/25/2004	Lakshman R. Schgal	3840-006-27	8149

7590 02/16/2006

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EXAMINER

PRIEBE, SCOTT DAVID

ART UNIT	PAPER NUMBER
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1633

DATE MAILED: 02/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 10/785,156	Applicant(s) SEHGAL ET AL.	
	Examiner Scott D. Priebe, Ph.D.	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 12 January 2006.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above claim(s) 10-14 and 16-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-9 and 15 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 25 February 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)</p> <p>2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)</p> <p>3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br/>Paper No(s)/Mail Date <u>20041119, 20050718</u>.</p> | <p>4) <input type="checkbox"/> Interview Summary (PTO-413)<br/>Paper No(s)/Mail Date. _____.</p> <p>5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)</p> <p>6) <input checked="" type="checkbox"/> Other: <u>IDS of 20050830</u>.</p> |
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## **DETAILED ACTION**

### ***Election/Restrictions***

Applicant's election with traverse of Group I, claims 3-5, in the reply filed on 1/12/06 is acknowledged. The traversal is on the ground(s) that there is no undue burden on the Examiner. This is not found persuasive because Applicant has provided no basis for their assertion that there would be no undue burden. In contrast, the Office action of 12/12/05 (page 3) indicated why there would be a search and examination burden.

The requirement is still deemed proper and is therefore made FINAL.

Claims 10-14 and 16-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/12/06.

### ***Information Disclosure Statement***

The information disclosure statement filed 11/19/04 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein as document DK, Kibbe et al., has not been considered. The document cited appears to be a book; however, all that was provided was a copy of the cover, title page, and publication information.

*Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for embodiments wherein the thrombomodulin coding sequence is operably linked to a promoter that mediates expression of TM in the mammal and wherein the thrombotic disease is atherosclerotic cardiovascular disease and the vector is administered locally to a vascular (vein or artery) site of thrombus (including an expected future site of thrombus), does not reasonably provide enablement for any other embodiments embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are broadly directed to the treatment by gene therapy of any type of thrombotic disease in a mammal by administration of a viral vector encoding TM (adenoviral vector has been elected) to the mammal by any route of administration to any target tissue, and do not require that the TM actually be expressed in the mammal or that the vector also comprise a promoter that directs expression in the mammal.

As a preliminary matter, the specification teaches that the basis for the therapy relies on the expression of TM from the vector. Consequently, embodiments, which are embraced by the claims as written, where the TM is not expressed in the mammal or where the vector does not comprise a promoter operable in the mammal and in operable linkage to the TM coding sequence are not enabled on their face since they are inoperable. See rejection under 35 USC 2<sup>nd</sup> para. below directed to this same issue.

The guidance in the specification pertaining to the claimed elected invention is limited to a description of human TM and definition of a human TM variant (page 8), a general description of various types of vector that can be used in the method (adenoviral vectors on pages 11-15), an overview of different types of promoters that can be used (pages 20-22); a general description of various routes of administration of the vector (most conceivable routes appears to be taught) and various pharmaceutical compositions in which the vector may be formulated for various routes (pages 26-31); and a listing of several different “thrombotic diseases” that might be treated (pages 32-33). The specification (page 32) teaches that in the case of atherosclerotic cardiovascular diseases, the vector should be administered locally to a vascular (vein or artery) site of thrombus formation, particularly associated with a variety of surgical procedures involved in treatment of these diseases. The specification (pages 32-33) merely suggests that the other thrombotic diseases listed in claim 9 can be treated, without providing any specific guidance as to the route of administration or target tissues or cells of such treatment or as to the therapeutic endpoint desired in treating these diseases. The specification provides no actual working examples of treating any disease or disease model with the claimed invention. Example 5 (prophetic) suggests that a gutless adenoviral vector will be administered to rodents. The

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specification does not, however, identify any relevant rodent models for any of the thrombotic diseases. This example acknowledges that the dose and route of viral vector administration will depend on the disease and its severity, but does not give any such guidance. The specification mentions various routes of administration, e.g. claim 15, but, with the exception of local vascular administration in the context of atherosclerotic cardiovascular diseases, does not teach when the other routes of administration are appropriate. The law under §112, first para. requires that the disclosure in the application shall inform those skilled in the art how to use the invention, not how to find out for themselves how to use it. *In re Gardner*, 166 USPQ 138, 141 (CCPA 1970).

At the time the invention was made, gene therapy in general was highly unpredictable and still largely undeveloped art, despite high skill in the art and extensive experimentation. Orkin et al. reviews the state of the art of gene therapy before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression that gene therapy is successful is mistaken (pages 1-2). Each of the defects in the gene therapy art as a whole cited by Orkin et al. applies to the instant invention. Verma et al. (Nature 389: 239-242, 1997) reiterates the finding in

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Orkin that not a single successful gene therapy protocol for humans had been described in the art and that lack of efficient gene delivery and sustained expression remained the Achilles heel of gene therapy (see page 239). The instant specification does not generally correct the deficiencies in the prior art regarding gene therapy. Rather, the specification relies upon the prior art for teaching expression constructs and nucleic acid vectors which have been tried, and some untried, which have not been successful in light of Orkin and Verma. Verma clearly discloses that serious problems existed in this art such that no unequivocal success had been obtained for the treatment of any disease. Verma reports optimism that the problems would be surmounted and that gene therapy would one day be routine, however, there is no evidence of record that it was routine at the time the invention was made, quite the contrary. Rosenberg et al. (Science 287: 1751, 2000) reported there was still no unequivocal instance of clinical efficacy with gene therapy, and that those in the field were still guilty of overselling gene therapy, despite a decade of failure. Orkin clearly makes the point that gene therapy for each disease would present its own scientific and clinical challenges.

Zuckerbraun (Arch. Surg. 137: 854-861, Jul. 2002) reviews vascular gene therapy shortly before the instant invention was made. Zuckerbraun makes clear that several hurdles remained to be overcome in the development of vascular gene therapy (page 854, col. 2), such as identifying a disease amenable to treatment by gene therapy and the accessibility of the target tissue. The latter implies that one must also know what the target tissues are. Zuckerbraun summarizes advances in the treatment of localized vascular defects or damage, such as encountered in treatment of atherosclerotic cardiovascular disease (page 857), and mentions gene therapy for preventing localized thrombosis (pages 859-860) following bypass surgery or angioplasty.

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Absent is any indication that those of skill in the art were aware of whether other thrombotic diseases, such as pulmonary hypertension, acute inflammatory diseases (sepsis), end-stage renal failure, or Alzheimer disease, were amenable to gene therapy with a TM gene or any other gene, what target tissues should be treated for these diseases, how the vector should be delivered to the target tissue effectively, or what the desired therapeutic endpoint of the treatment would be. The instant specification provides no guidance on these matters.

With respect to treatment of acute inflammatory diseases, e.g. sepsis, Esmon (Ann. Med. 34: 598-605, 2002) reviews the involvement of the Protein C pathway in sepsis. It teaches that this pathway is complex and involves interaction between a variety of different proteins (Fig. 1), and TM serves as a molecular switch in the process (page 34). Inflammation leads to the downregulation of TM; endothelial protein C receptor, which accelerates protein C activation by TM; and protein C expression (pages 601, col. 1-2; 602, col. 2); and to the inactivation and cleaving of TM from the endothelial cell surface to produce soluble TM, which is much less active than its membrane bound form. All of these events lead to a decrease in protein C activation and impair the pathway. Given that TM is not the only key component of the protein C pathway that is negatively affected in inflammation and sepsis, it is unclear whether TM gene therapy would be effective or how the treatment should be carried out to produce a therapeutic effect.

With respect to treatment of Alzheimer's disease, Borroni et al. (Alzheimer's Disease and Associated Disorders 16(3): 150-155, 2002) is the only prior art identified disclosing any sort of vascular involvement in Alzheimer's disease relating to TM, and does not disclose that thrombosis is a problem. This disease is characterized in early stages by increased expression of



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thrombomodulin (pages 153-154), and it is unclear how further temporary increase in thrombomodulin expression, by transfection, would have any effect at all, except perhaps to further exacerbate any abnormalities, if any, caused by the elevated thrombomodulin levels already associated with early stages of Alzheimer's.

Consequently, in view of the breadth of the claims, the limited guidance presented in the specification and lack of relevant working examples, the unpredictability of gene therapy in general, the limited guidance in the prior art and indication that obstacles still existed in vascular gene therapy, it would have required undue experimentation to practice the claimed invention as broadly as it is claimed.

Claims 1-9 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9 and 15 are incomplete, since the goal of the method as set forth in the preamble is not reflected in the limitations recited in the active process step recited. In light of the specification, it appears that the treatment results from expression of the thrombomodulin, TM, from the vector in transfected cells following administration to the mammal. None of the claims require expression of TM. Except for claims 6-8, the vector is not even required to comprise sequences necessary for expression. In claims 6-8, although the presence of a promoter operably linked to the TM coding sequence is indicated, the promoter need not be one operable in mammals. Amending claim 1 to indicate that the TM is expressed in the mammal, for example, would overcome this part of the rejection.

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Claim 4 is directed to an embodiment of the method wherein the vector is a gutless adenoviral vector “produced using a shuttle vector comprising the nucleotide sequence recited in SEQ ID NO: 4.” The claim does not recite any positive process in which the “shuttle vector” is used to make the adenoviral vector. Consequently, it is unclear how the shuttle vector is used, or what the resulting adenoviral vector is. The specification describes gutless adenoviral vectors that comprise the nucleotide sequence of SEQ ID NO: 4. If this is what the claim is intended to cover, it is suggested that it be amended to describe the content of the gutless adenoviral viral directly, instead of indirectly by reference to some unspecified process used to make it.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 6-9, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Bach et al., WO 96/06933.

Bach et al. discloses a method for treating thrombosis, including that associated with systemic or local inflammatory conditions, in a mammal by administering an expression vector to the affected tissue that encodes thrombomodulin, wherein the thrombomodulin coding sequence is operably linked to a constitutive, tissue-specific or regulatable promoter (pages 3-4, 9, 13, claims 2-10). More specifically, adenoviral vectors can be used (pages 6, 11-13), and the thrombomodulin is human thrombomodulin (page 15).

Claims 1-3, 6, 9 and 15 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Waugh et al. (Circulation 102(3): 332-337, July 2000).

Waugh discloses a method for treating restenosis by administering an adenoviral vector encoding human thrombomodulin under control of a constitutive RSV promoter to the location of an artery where restenosis, which includes thrombosis, may occur (see entire reference, especially, abstract for overview, and page 333, col. 1).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Bach et al., WO 96/06933, as applied to claims 1-3, 6-9, and 15 above or Waugh et al. (Circulation 102(3): 332-337, July 2000) as applied to claims 1-3, 6, 9, and 15 above, and further in view of Vassalli et al. (Cardiovasc. Res. 35: 459-469, 1999) and Umana et al. (Nat. Biotech. 19(6): 582-585, Jun. 2001).

Bach and Waugh have been described above. Neither teach to use a gutless adenovirus.

However, Vassalli teaches that while adenoviral vectors are the vector of choice for vascular gene therapy, their use is limited by short transgene expression due to T-cell mediated response to transfected cells in response to expression of viral proteins. Vassalli (page 460) suggests that adenoviral vectors lacking all viral genes, i.e. gutless adenoviral vectors, may minimize or eliminate this problem, and that early results showed this result. Umana, published years after Vassalli, details how to make sufficient quantities of gutless adenoviral vectors, and reiterates that gutless vectors mediate long term expression (see abstract).

Therefore, it would have been obvious to one of skill in the art to have utilized a gutless adenovirus in the methods of Bach or Waugh to take advantage of the longer expression times afforded by gutless adenoviral vectors as compared to the older adenoviral vectors used in Bach and Waugh.

### ***Conclusion***

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Sehgal et al., US 2004/0198683, discloses and claims a method readable on the instant invention (see claims 14-25). It is not prior art under 35 USC 102(e) because it is not

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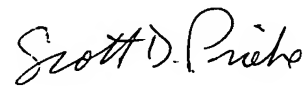
deemed to meet the requirements of 35 USC 119(e) for benefit of priority. Although a rejection of the instant claims for obviousness-type double patenting has not been made because claims 14-25 are non-elected, such a rejection may be necessitated should the restriction requirement be withdrawn.

To the extent that claim 5 was intended to indicate that the adenoviral vector comprised SEQ ID NO: 4, no prior art was found that suggested or disclosed this particular expression cassette.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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Art Unit 1633